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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

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ART UNIT	PAPER NUMBER
1644	31

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 4/27/98

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-20, 28, 29, 32-34, 36-40 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-20, 28, 29, 32-34, 36-40 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PA

15. Applicants' election of claims 1-20, 28-29, 32, 33, 34, and 36-40 is noted. Applicants' urge that since the claims are allowable, all claims must now be examined. The Examiner has not determined that any claims are allowable, therefore the claims currently under consideration are 1-20, 28-29, 32, 33, 34, and 36-40. Claims 21-27, 30-31, and 35 stand withdrawn from consideration. Applicants' request to hold the drawing requirements in abeyance until such time as allowable subject matter is identified is noted. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior office action.

16. Claims 1-20, 28-29, 32-34, and 36-40 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48, 50, 51 and 54 of copending application Serial No. 07/492460 in view of Wu et al., (AC1), Knapp et al., Goers et al. ('973). and Rossi et al. Applicant's traversal appears to be over the following grounds: 1) The claims of the '460 application do not suggest the claims of the instantly claimed invention, and 2) "... the Examiner provides nothing more than a broad series of suggestions "to try" a great variety of possibilities. Applicants' traversal has been considered but is not found persuasive for the following reasons. In the establishment of an obviousness-type double patenting rejection, the Examiner must make a determination on who represents those skilled in the art. In the case of the instant invention, it would be those individuals who engage in the production of transfection vehicles such as the claimed protein-polycation complexes and use such vehicles in the transfection of cells. Accordingly, the determination of the Examiner is that one of ordinary skill in the art would recognize that where the introduction of nucleic acids, such as ribozymes, into T-cells is desired, one of ordinary skill would necessarily utilize proteins, such as gp120 or antibodies to T-cell proteins known to be capable of initiating endocytosis, in order to facilitate the introduction of DNA into the target cells. It is the target cell that dictates what the targeting agent will be, this is a fact that would have been readily recognized by the routineer. Furthermore, it was known in the art that CD4 and CD7 specific antibodies were capable of inducing endocytosis into T-cells (see Carriere et al.). In view of these reasons, Applicants' arguments have not been found persuasive.

17. Claims 1-20, 28-29, 32-34, and 36-40 stand rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. Applicant specifically argues that the Examiner recognizes an ex vivo utility for the invention. The Examiner has made no such recognition. Applicant has used a sentence out of its context in an effort to support an undisclosed utility for the invention. There has been no apparent contemplation of the use of the claimed invention in an ex vivo manner by Applicant. Furthermore, the sentence referred to by Applicant was made in reference to known chloroquin toxicity to mammalian cells, not to a possible utility of Applicants' invention recognized by the Examiner. The utility of a given invention is that which is contemplated by Applicant. The Examiner is in no position to give a

utility to any given invention. Applicant's arguments have been considered but are not found persuasive for the reasons of record.

18. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention. The specification is objected to for the following reasons:

A) Applicants have not disclosed how to use the claimed compositions, complexes, and processes therapeutically in humans. There is insufficient written description of the invention with respect to the in vivo operability of the invention as a therapeutic agent suitable for the treatment of humans for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 24). Applicant also claims protein-A-polycation conjugates which would be useful for targeting nucleic acid into cells. This embodiment is not believed to be operable because no mechanism exists to prevent the administered protein-A-polycation-nucleic acid complex from bind serum IgG rather than target bound IgG in vivo. Upon administration to the patient, the protein-A will complex to IgG circulating in the vascular system and will, in all likelihood, be unable to reach the target site.

19. Claims 1-20, 28-29, 32-34, and 36-40 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see paragraph 26). Applicant's arguments have been considered but are not found persuasive for the following reason: 1) Applicant argues that the claims are not limited to the in vivo use of the invention. Applicant's specification specifically recites contemplated uses of the claimed invention as therapeutic modalities suitable for in vivo use.

20. Claims 1, 6, 11, 13-16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wagner et al. (AT2). This rejection has been withdrawn because of Applicant's amendments to the claims.

21. Claims 17, 18, 36, and 38 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Wagner et al. (AT2). Wagner et al. teach transferrin-polycation complexes which are capable of introducing nucleic acids into T-cells. The art recognizes that transferrin receptors are found on a variety of cells and that these receptors are identified as CD71 or OKT9 in the art (see the supplied CD guide). It is also known that transferrin receptor concentration is increased on metastic cells and is found on T-cells. Applicant does not appear to have addressed this grounds of rejection.

22. Claims 2-5, 7-10, 12, 37 and 39-40 stand rejected under 35 U.S.C. § 103 as being

unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al.

23. **RESPONSE TO TRAVERSAL:** Applicants' arguments have been considered but are not found persuasive for the following reasons. Applicant traverses on the grounds that the combination of references fails to teach or suggest the combination of references. It is what the combination of references teaches to one of ordinary skill and a determination of who one of ordinary skill was at the time of invention which renders the claimed invention obvious. As stated earlier, the determination of the routineer for the purposes of this invention is held to be one who constructs and uses protein polycation complexes in transformation techniques. At issue in the instantly claimed invention is the following: Is Applicants' invention, namely proteins which are able to deliver nucleic acids specifically into T-cell rendered obvious to those skilled in the art based on the combination of references and in view of the skill level at the time of invention? It is the position of the Examiner that the combination renders the invention obvious for the following reasons: 1) The art recognized the potential of nucleotide analogues for the treatment of a variety of diseases, including HIV infection (see Applicants' admitted prior art Zon et al., especially pages 545-546) and 2) Antibodies which specifically directed materials into T-cells were known in the art well before the earliest priority date of Applicant (see Cafiere et al.). Those skilled in the art are presumed to be familiar with any and all references related to the claimed invention and the question of obviousness remains that do the combined references suggest the invention to one of ordinary skill in the art at the time of invention. Where the routineer sought to introduce nucleic acids into T-cells, it is the position of the Examiner that the combination does, in fact, render the claimed invention obvious. Applicants' comments over the antibody-protein A-polycation complex is noted. Although not explicitly stated, the Examiner intended to explain that the coupling of protein A to the polycations would have allowed for the generation of antibody-protein A-polycation complexes that could bind to any desired cell surface component which allowed for the internalization of the complex. Those skilled in the art would have recognized that the protein A-polycation complex could be attached to any IgG molecule of the appropriate targeting specificity by virtue of the known protein A binding capability to IgG molecules. Applicant also appears to traverse on the grounds that improper hindsight was used in the evaluation of the claimed invention. The Examiner would respectfully disagree. It should be pointed out that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught with regard to the claimed material, In re Nilssen, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). In response to Applicants' argument that the Examiners conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include

knowledge gleaned only from the Applicants' disclosure, such a reconstruction is proper, In re McLaughlin, 443 F.2d 1392; 170 USPQ 209 (CCPA 1971).

24. Claims 28-29 and 32-34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. and Haseloff et al., or Rossi et al. ('019).

25. **RESPONSE TO TRAVERSAL:** Applicants' traversal covers, essentially, the same ground as that in the previous traversal on the first 103 rejection set forth by the Examiner. Applicants' arguments have been considered but are not found persuasive for the following reasons: 1) Applicants' traversal on the arguments presented in the first 103 rejection (paragraph 31, paper #7) are not found persuasive for the reasons set forth above in paragraph #23) Applicant argues that there is no motivation to target ribozymes to T-cells based on the combination of references. Again, it should be pointed out that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught with regard to the claimed material, In re Nilssen, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). Ribozymes were known to be capable of degrading the mRNA of a variety of genes. Haseloff et al. teach that synthetic ribozymes can be constructed to inactivate the RNA of any particular gene, given that the sequence is known (see pages 591-592). Rossi et al. teach that HIV-1 specific ribozymes were known before the time of the invention of the claimed subject matter. In view of the combined references, it is the conclusion of the Examiner that one could reasonably expect to arrive at the claimed invention because those skilled in the art recognized the usefulness of introducing ribozymes into target cells and also recognized and knew those antibodies useful in targeting materials into T-cells. The construction of proteins-polycation conjugates according to the claimed invention was within the skill level of the routineer and one of ordinary skill would have been motivated to construct such products because they would have been useful for the introduction of nucleic acids into cells in a manner directly analogous to that of Wu et al. or Wagner et al. Applicants' arguments have been considered but are not found persuasive.

NEW GROUNDS OF REJECTION

26. Claims 1, 3-7, and 11-16 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. and Cafiere et al. Claims 1, 3-7, and 11-16 are drawn to protein-polycation complexes capable of binding to cell surface proteins other than the transferrin receptor to facilitate internalization and also capable of binding nucleic acids, such as antibodies or other proteins which specifically bind CD4 or CD7 and initiate endocytosis. Wu et al. teach a method of transfecting hepatocytes using asialoproteins conjugated to polycations for the transfection of liver cells (see abstract and column 4, paragraph 2). Wagner et al. teach the use of transferrin-polycation

conjugates for the transfection of cells with DNA including the use of polylysine and protamine. Wu et al. teach a number of polycationic molecules useful in the instant invention, including histones, polylysine, etc (column 4, paragraph 2). Wu et al. teach that other targeting agents (i.e. hormones or antibodies) may be used to direct the conjugates to the target cell (see columns 5-6, The nature of the Ligand) and that agent used will depend upon the target cell. The references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells. Goers et al. teach that therapeutic agents are selected for their intended application. Where the targeting of DNA to only T-cells is contemplated, antibodies specific for T-cell antigens would be selected. Knapp et al. teach a variety of known T-cell specific antibodies which are commercially available. The substitution of such antibodies as targeting agents of protein-polycation complexes would have been obvious to one of ordinary skill where the targeting of T-cell was desired. Cabiere et al. teach a number of monoclonal antibodies known to be internalized into T-cells upon their binding of specific antigen, including CD4 and CD7 specific antibodies. GP120 is known to initiate endocytosis into T-cells by contacting CD4. One of ordinary skill would have recognized that the use of antibodies such as those described in Cabiere et al. would have allowed for the introduction of nucleic acids in to T-cells when the antibodies or gp120 were attached to polycation complexes such as those of Wu et al. or Wagner et al. instead of transferrin.

One of ordinary skill in the art at the time the invention was made would have been motivated to select proteins which specifically targeted T-cells for protein-polycation conjugates because such proteins would have allowed for the specific direction and introduction of nucleic acid laden conjugates to T-cells. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

27. No claim is allowed. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE

ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

28. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Eisenschenk whose telephone number is (703) 308-0452. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Christopher Eisenschenk, Ph.D.
May 23, 1994

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180

5/27/94